

Review Article

Irisin: linking metabolism with heart failure

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Abstract: The heart is an organ with extremely high energy expenditure, and cardiac performance is consistent with its metabolic level. Under pathological situations, the heart adjusts its metabolic pattern through mitochondrial regulation and substrate selection to maintain energy homeostasis. Heart failure is associated with impaired cardiac energy production, transduction or utilization. Reduced exercise tolerance, skeletal muscle dystrophy and even cardiac cachexia are commonly found in patients with advanced heart failure. Irisin is a newly identified myokine and is mainly secreted by skeletal muscles after exercise. Irisin regulates metabolism and plays essential roles in the development of metabolic diseases. The heart is another abundant source of irisin synthesis and secretion other than skeletal muscle. However, the functions of irisin in the heart have not been completely elucidated. This review introduces the current understanding of the physiological role of irisin, alteration of irisin levels in heart failure, possible mechanisms of irisin in metabolic remodeling and cardiac hypertrophy, and perspectives of irisin serving as a novel target in the management of heart failure.

Keywords: Irisin, metabolism, heart failure, fibronectin type III domain containing protein 5, reactive oxygen species

Introduction

Heart failure (HF) occurs when cardiac output fails to fulfill the metabolic demands of the body, even with compensatory neurohormonal activation. HF could be the terminal stage of various types of cardiovascular disorders. It is reported that HF affects 26 million people worldwide [1] with an estimated annual mortality rate of 10% [2]. Adenosine triphosphate (ATP) production and turnover are robust in the mitochondria of cardiomyocytes to meet the energy demand and maintain the mechanical function of the heart. The heart has a complex network to regulate metabolism by utilizing different substrates or metabolic intermediates for oxidative phosphorylation (OXPHOS) or glycolysis. Impaired energy production is associated with the development and progress of HF, and metabolic remodeling has been recognized as a novel target for HF treatment in animal models and translational studies [3].

Irisin is a recently discovered 112-amino acid myokine that is proteolytic cleaved from its pre-

cursor fibronectin type III domain-containing protein 5 (FNDC5). Irisin plays an essential role in fat metabolism and energy homeostasis through the browning of white adipose tissue [4, 5]. This myokine is mainly secreted by skeletal muscle after exercise, especially upon the activation of peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), and exhibits great therapeutic potential in metabolic diseases, such as obesity, insulin resistance and diabetes mellitus [6, 7]. In addition to skeletal muscles, cardiac muscles consistently produce high levels of irisin even without exercise [8], indicating a substantial role of irisin in cardiac physiology. The heart is a high-energy demanding organ. Cardiac metabolic levels determine the function and fate of cardiomyocytes [9], and persistent metabolic abnormalities lead to heart failure [10]. Circulating irisin levels were associated with the clinical outcome in a heart failure population [11, 12]. Given its involvement in both metabolic regulation and heart failure, irisin might serve as a connector between metabolism and heart failure. Here, in this review, we would like to introduce the cur-

rent understanding of the physiological role of irisin in the heart, alteration of irisin levels in heart failure, mechanism of irisin in metabolic remodeling and cardiac hypertrophy, and the perspectives of irisin serving as a novel target in the management of heart failure.

Alteration of energy metabolism in the failing heart

Although the heart consumes an extremely high amount of ATP every day, its reservoir of ATP is relatively limited and could be depleted within seconds [13]. Cardiac mitochondria produce over 90% of the required ATP through OXPHOS, whereas the other ATP are obtained from glycolysis and Krebs cycle. To meet the constant energy demand, mitochondrial content in the heart is the highest in the human body. Inside the mitochondria, energy transmitted through hydrolysis of ATP could also be stored in the form of high-energy phosphocreatine (PCr) [3], and the phosphocreatine to ATP ratio (PCr/ATP) measured by ^{31}P magnetic resonance spectroscopy (^{31}P -MRS) has been broadly applied as a noninvasive imaging tool in evaluating cardiac metabolic conditions. Morphological abnormalities of mitochondria, such as increased number, reduced size and compromised structural integrity, are found in patients with chronic heart failure [14] as a sign of long-lasting energy deficiency. Some previously published review papers have thoroughly discussed mitochondrial dysfunction and metabolic changes in heart failure [15-17].

Mitochondria are capable of utilizing various classes of substrates, such as lipids, carbohydrates, amino acids, and ketone bodies, for ATP production [9]. Different metabolic substrates have different ATP yields, and free fatty acids (FFAs) have the highest ATP yield. In the healthy adult heart, β -oxidation of FFAs accounted for approximately 70% of energy production followed by glucose metabolism [18]. If changes occurred in cardiac workload and/or substrate availability, the heart could shift reliance from one substrate to another for ATP replenishment, which is termed as metabolic flexibility [19]. Although glucose metabolism provides less ATP yield per molecule than lipids, it has a greater efficiency in producing high energy phosphates; thus, glucose oxidation consumes less oxygen for equivalent ATP synthesized compared to fatty acid oxidation (FAO) [20].

Lipid and glucose metabolism are tightly connected in a competitive manner; thus, excessive utilization of one substrate will inevitably inhibit the other substrates as noted in the glucose fatty-acid cycle (the Randle cycle) [21]. Disturbed substrate selection of FFAs and glucose is highly relevant in the pathophysiology of cardiac disease [22]. Reduced FAO, increased glucose and ketone bodies utilization were found in the failing heart either in an acute phase or chronic condition [18, 23]. Accumulating evidence suggests that irisin regulates substrate metabolism in skeletal muscle cells and hepatic cells [24, 25], but no study has assessed its role in cardiomyocytes. Through *in vitro* models of primary cultured adult cardiomyocytes or H9c2 cardioblast cells, it will be crucial to understand the following questions: 1) Is there any difference in substrate selection and utilization in cardiomyocytes in the presence or absence of irisin? 2) Are irisin synthesis and secretion in cardiomyocytes affected by exogenous stimuli, such as hypoxia or glucose deprivation? 3) What is the optimal range of irisin levels in regulating cardiomyocyte metabolism?

Moreover, one should recognize that these substrates and their metabolic intermediates are not just fueling the heart but also actively involved in the complex network of signal transduction, oxidative stress, and transcriptional regulation. Acute lack of energy in the heart activates the adenosine monophosphate-activated protein kinase (AMPK) pathway and facilitates FAO via phosphorylation and inactivation of acetyl-CoA carboxylase 2 (ACC2) [26], but it also leads to glycogen accumulation and cardiac hypertrophy [27]. More signaling molecules are activated when the heart suffers from a long-term scarcity of energy, includes peroxisome proliferator-activated receptors (PPAR), nuclear respiratory factors (NRF), estrogen-related receptors (ERR α and ERR γ), and PGC-1 α [28], to balance the metabolic pattern and help to correct cell stress and signal transduction. Thus, metabolic modulation has been raised as a promising therapeutic target for heart failure [29].

Roles of irisin in metabolic balance

Since its discovery, irisin was spotlighted by the scientific community for its therapeutic potential in metabolic-related disorders, such as obe-

sity and type 2 diabetes mellitus (T2DM) [30, 31]. As the precursor of irisin, FNDC5 comprises a signaling peptide, a fibronectin type III domain, and a C-terminal hydrophobic domain, which is anchored in the cell membrane. FNDC5 is abundantly expressed in the heart, brain, liver and skeletal muscle, and is essential for maintaining metabolic homeostasis [32]. Experimental studies demonstrated that FNDC5 is actively involved in metabolic regulation through diverse upstream and downstream signaling pathways. When the N-terminal signal peptide is removed, FNDC5 is cleaved at the C-terminal, glycosylated and released into circulation in the form of irisin, which is named after the Greek messenger goddess Iris [4]. Irisin peptide structures are highly conserved among species [33].

Based on the findings of FNDC5 in metabolic regulation and the feature that irisin is secreted after exercise, researchers started to look at the role of irisin in thermogenesis. Boström et al. found that irisin stimulates uncoupling protein mRNA 1 (UCP1) expression and causes browning of white adipose cells from subcutaneous and visceral adipose tissues, thus promoting thermogenesis [4]. In addition, a mild increase in circulating irisin levels in mice results in accelerated energy expenditure independently from exercise or diet, indicating a protective potential for diet-induced obesity and insulin resistance [4]. In an *in vitro* experiment, Vaughan et al. noted that irisin-treated myocytes exhibited significantly increased oxidative metabolism and mitochondrial biogenesis along with significantly elevated metabolic gene expression, such as PGC-1 α , nuclear respiratory factor 1 (NRF1), mitochondrial transcription factor A (TFAM), glucose transporter 4 (GLUT4) and mitochondrial uncoupling protein 3 (UCP3) [34]. Zhang et al. demonstrated that recombinant irisin treatment in mice decreased body weight and improved glucose homeostasis by upregulating UCP1 expression through the p38 mitogen-activated protein kinase (p38-MAPK) pathway [35]. Huh et al. reported that irisin treatment enhances glucose and fatty acid uptake and metabolism in human skeletal muscle cells through adenosine monophosphate-activated protein kinase (AMPK) phosphorylation [36]. In summary, irisin is capable of increasing energy expenditure and decreasing insulin resistance.

Researchers found that exercise can increase circulating irisin levels in individuals with or without metabolic syndrome [37], and exercise-induced irisin secretion is beneficial for ambulatory capacity in humans [38]. Irisin was also found to be one of the crucial messengers in neuro-muscular crosstalk given that exercise upregulated the PGC-1 α /BDNF pathway (muscle/brain) through the signaling of circulating irisin, which strengthens synapses and exhibits neuroprotective and antidepressant effects [39]. Kim et al. studied the effect of aerobic training and resistance training on circulating irisin levels and their association with the changes in body composition in overweight/obese adults, demonstrating that resistance training had a more significant increase in circulating irisin levels as well as an improved positive change in body composition [40]. However, controversial results were found when applying circulating irisin levels as a biomarker for obesity and metabolic syndrome. Huh et al. measured circulating irisin levels in a cross-sectional study including 117 healthy middle-aged women and 14 obese subjects and found that circulating irisin levels were positively correlated with biceps circumference (as a surrogate marker for "lean" muscle mass), body mass index (BMI), glucose, ghrelin, and insulin-like growth factor 1 (IGF-1). In contrast, irisin levels were negatively correlated with age, insulin, cholesterol, and adiponectin levels. Multivariate regression analysis revealed that biceps circumference was the strongest predictor of circulating irisin levels underlying the association between irisin and metabolic factors in humans at baseline [41]. Several studies noted that circulating irisin levels are increased in the obese population compared with the normal-weight population and anorexic population, and irisin has a positive correlation with body weight and BMI [42, 43]. However, some studies revealed a negative association between circulating irisin levels and BMI [44, 45].

The inconsistency in associations between circulating irisin levels and BMI might arise from the differences in body composition. Irisin is mainly secreted by skeletal muscles after exercise, so the muscle mass is the determining factor for irisin levels. People with the same BMI might have significantly different body compositions or daily exercise levels. Thus, it will be more reasonable to perform regression

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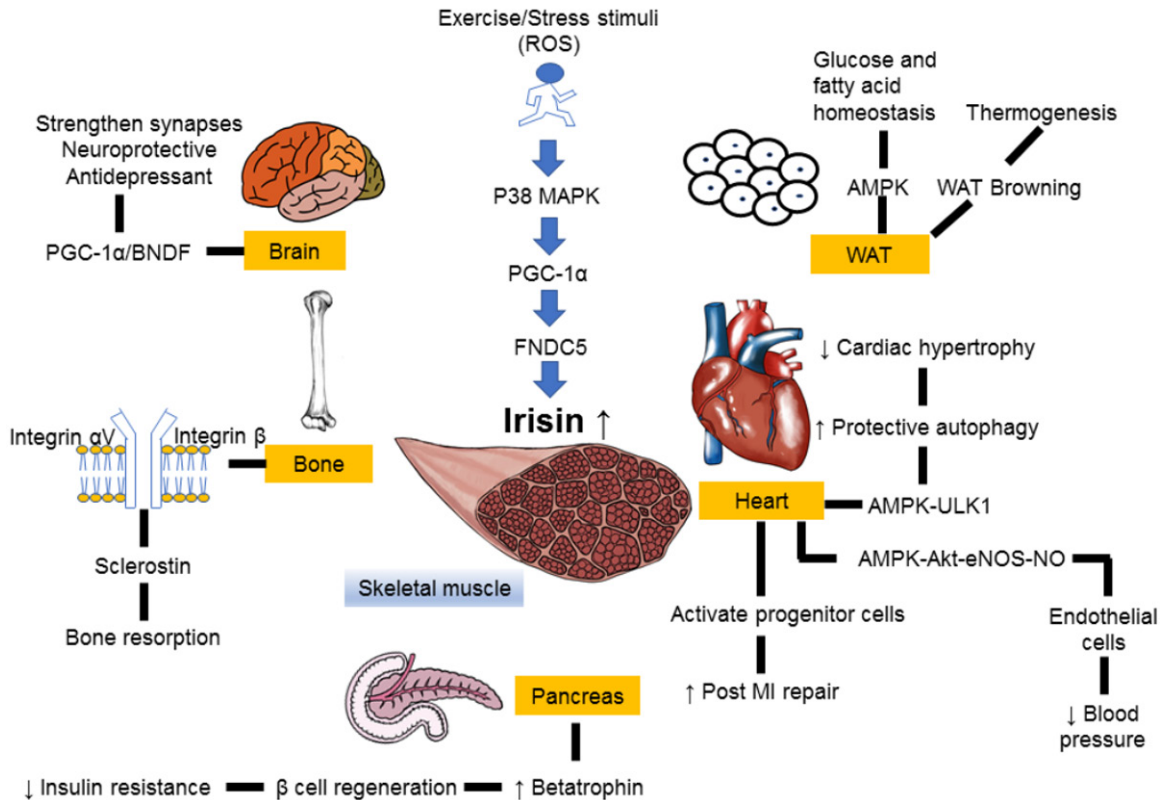


Figure 1. Regulatory roles of irisin in metabolic disorders. Irisin, the exercise-induced myokine, regulates the physiological and pathophysiological processes in various organs. (ROS, reactive oxygen species; P38 MAPK, p38 mitogen-activated protein kinase; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 α ; FNDC5, fibronectin type III domain containing protein 5; WAT, white adipose tissues; AMPK, adenosine monophosphate-activated protein kinase; ULK1, serine/threonine-protein kinase; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; MI, myocardial infarction; BDNF, brain derived neurotrophic factor).

analysis of circulating irisin levels with age, skeletal muscle mass index (SMI), and daily exercise level. We also need to recognize the heterogeneity of obesity and metabolic syndrome, such as diabetic population versus non-diabetic population, type 1 diabetic mellitus versus type 2 diabetes mellitus, and familial metabolic disorder versus diet-induced obesity, and future results from prospective cohort studies or longitudinal registries instead of cross-sectional studies are required. A schematic summary of the roles of irisin in metabolic disorders was presented in **Figure 1**.

Roles of irisin in heart failure

Studies that described the alteration of circulating FNDC5/irisin levels in heart failure cohorts are listed in **Table 1**, and experimental studies examining the roles of FNDC5/irisin in the development and progression of heart failure are shown in **Table 2**. Given that the heart

is an organ with extremely high energy expenditure and high FNDC5 expression, it would be reasonable to study the role of irisin in the heart. Sundarajan et al. reported that irisin regulates cardiac physiology in zebrafish [46]. Exogenous irisin treatment increased diastolic volume, heart rate, and cardiac output, whereas irisin knockdown yielded opposing effects on cardiovascular function [46]. Dun et al. first reported the expression of irisin in cardiomyocytes through staining [47]. Gür et al. also demonstrated the presence of irisin in the cytoplasm of cardiomyocytes through immunostaining [48]. In a rat model, Shirvani et al. found that exercise training significantly increases plasma levels of irisin, which was consistent with the enhanced metabolic level [49]. Interestingly, age serves as a significant confounder in analyses of circulating irisin levels. Aydin et al. measured irisin expression both in serum and in supernatant from the cardiac muscle. Serum irisin levels increased after exercise and

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Table 1. Prospective cohort studies about FNDC5/irisin levels in the population with heart failure

Authors	Year	Population	Area	Size	LVEF/NYHA Classification	Findings
Lecker et al. [67]	2012	Systolic HF	USA	15/9	High vs low aerobic performance: 28.6±8.4% vs 31.3±6.4%	↑ FNDC5 expression in high aerobic performance group
Shen et al. [11]	2017	Acute HF	China	161	Irisin level low vs high: 43±15% vs 44±15%	↑ Irisin level associated with 1-year all-cause mortality
Kalkan et al. [69]	2018	HFrEF	Turkey	44/42	Cachectic vs noncachectic: NYHA III & IV vs NYHA I & II	↑↑ Irisin level in HF with cachexia
Abd El-Mottaleb et al. [70]	2019	MI with or without HF	Egypt	33/33	MI vs MI with HF: 52.97±0.92% vs 35.42±0.82%	↑ Irisin level in MI with HF comparing to MI without HF
Silvestrini et al. [12]	2019	HFpEF and HFrEF	Italy	22/18	HFpEF vs HFrEF: 56.7±1.3% vs 36.7±2.7%	↑↑ Irisin level in HFpEF comparing to HFrEF
Sobieszek et al. [71]	2020	Cachectic women with Chronic HF	Poland	34/32	Cachectic vs noncachectic: 42±13% vs 48±9%	↓ Irisin level in cachectic comparing to noncachectic group

Abbreviations: HF: heart failure; MI: myocardial infarction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association.

Table 2. Experimental studies suggesting the roles of FNDC5/irisin in heart failure

Authors	Year	Models	Findings	Pathways
Matsuo et al. [53]	2015	Rat ischemic cardiomyopathy ApoE ^{-/-} mice infused with Ang II	↓↓ FNDC5 and PGC-1 α expression in ischemic cardiomyopathy ↓ Circulating irisin level in CHF	TNF- α , IL-1 β , and/or Ang II
Peng et al. [57]	2017	H ₂ O ₂ -induced apoptosis in H9c2 cardiomyoblasts	Irisin treatment ↑ cell viability, ↓ ROS and ↓ apoptosis in a dose-dependent manner	miR-19b/PTEN/AKT/mTOR
Li et al. [58]	2019	Pressure overload by TAC in mice Ang II-induced apoptosis in cardiomyocytes	Overexpression of irisin ↓ myocardial hypertrophy and ↓ cardiomyocytes apoptosis	Irisin-induced protective autophagy and alleviated apoptosis signaling
Li et al. [59]	2018	Pressure overload by TAC in mice Ang II/PE-induced injury in cardiomyocytes	FNDC5 deficiency aggravated and FNDC5 overexpression attenuated TAC-induced cardiac hypertrophy Irisin attenuate cardiomyocyte hypertrophy induced by Ang II/PE	AMPK-ULK1

Abbreviations: ApoE: apolipoprotein E; TNF- α : tumor necrosis factor- α ; IL-1 β : interleukin-1 β ; Ang II: angiotensin II; TAC: transverse aortic constriction; PE: phenylephrine.

were higher in younger (12 months) than older (24 months) rats. However, irisin levels in myocardial supernatant remain high regardless of whether exercise is performed [8]. Belviranlı et al. also reported that exercise training increases cardiac and plasma levels of irisin in young and aged rats, but the average irisin level was relatively lower in the aged sedentary group [50]. Zhao et al. conducted an investigation on the effect of irisin on cardiac progenitor cell (CPC)-induced cardiac repair and function improvement, and found irisin treatment enhanced cardiac regeneration and neovascularization by promoting Nkx2.5+ CPCs engraftment [51]. Irisin-associated metabolic modulation might be another aspect for us to understand the process of aging.

Cardiac ischemia or heart failure commonly leads to insufficient energy production. A lower irisin level might be beneficial by suppressing browning of white adipose tissue, thus maintaining energy homeostasis. Kuloglu et al. found that serum irisin levels gradually decreased from 1 to 24 hours in a rat model of myocardial infarction (MI) compared with the control group [52]. Matsuo et al. reported reduced expression of skeletal muscle FNDC5 and reduced circulating irisin levels in rats with chronic heart failure induced by cardiac ischemia [53]. Wang et al. administered exogenous irisin in a rat MI model and found that irisin protects the heart from ischemia/reperfusion (I/R) injury in a dose-dependent manner [54]. Decreased blood pressure after irisin treatment was observed in a spontaneously hypertensive rat model through invasive recordings in the carotid artery, and improvement in endothelial dysfunction occurred via the AMPK-Akt-eNOS-NO pathway [55]. Liao et al. administered irisin for two weeks in a mice MI model and found that irisin improved cardiac function, attenuated ventricular dilation, and reduced infarct size at four weeks after MI [56]. Xie et al. used recombinant irisin to treat cardiomyoblast (H9c2) cells and found that irisin inhibited cell proliferation and activated metabolic and differentiation-associated genes, such as myocardin, follistatin, smooth muscle actin, and nuclear respiratory factor-1. Peng et al. reported that irisin attenuated hydrogen peroxide (H₂O₂)-induced cardiomyocyte apoptosis via the microRNA-19b/AKT/mTOR signaling pathway [57]. Li et al. studied the effect of irisin on cardiac hyper-

trophy in different models, including angiotensin II (Ang II) or phenylephrine (PE)-treated cardiomyocytes or a mouse transverse aortic constriction (TAC) model, and verified that irisin mitigates cardiac hypertrophy through regulating autophagy via mTOR-independent activation of the AMPK-ULK1 pathway [58, 59]. Irisin also activated intracellular Ca²⁺ signaling and increased cellular oxygen consumption in H9C2 cells [60]. Zhao et al. reported the protective effect of irisin on H9C2 cells exposed to hypoxia/reoxygenation injury, partially through the modulation of histone deacetylase 4 (HDAC4) [61]. Wang et al. studied the effect of irisin on an *in vitro* model of myocardial ischemia/reperfusion injury. Irisin treatment reduced myocardial infarct size in the Langendorff perfused heart and increased SOD-1 and p38 phosphorylation. Reduced lactate dehydrogenase (LDH) levels and attenuated cell apoptosis were observed in H9C2 cells treated with recombinant irisin along with preserved mitochondria function as indicated by mitochondrial permeability transition pore (mPTP) opening and mitochondrial swelling [62]. However, the timing of irisin administration could be tricky in the setting of myocardial infarction. For example, during the acute phase of myocardial infarction, limiting cell damage and compensating cardiac function is the priority. However, in the chronic remodeling process, we will pay more attention to the regulation of cell proliferation and controlling reactive oxygen species (ROS) production. Thus, a more detailed schema of changes in irisin levels and metabolic patterns after myocardial infarction will aid in the development of intervening measures.

Mechanisms of the protective effect from irisin treatment have not been completely elucidated. Previous studies reported various mechanisms, including reduced cell apoptosis, increased angiogenesis, inhibited cell proliferation, attenuated ROS production, augmented calcium signaling, improved mitochondrial function, altered metabolic profile, and oxygen consumption, as summarized in **Figure 2**. Moreover, it might be premature to conclude the effect of irisin as 'protective'. Ho et al. overexpressed the *Fndc5* gene in C57BL6/J mice through adenovirus transduction and significantly increased expression of irisin was found in the heart and liver ten days after tail vein injection. An elevated cardiac mitochondrial

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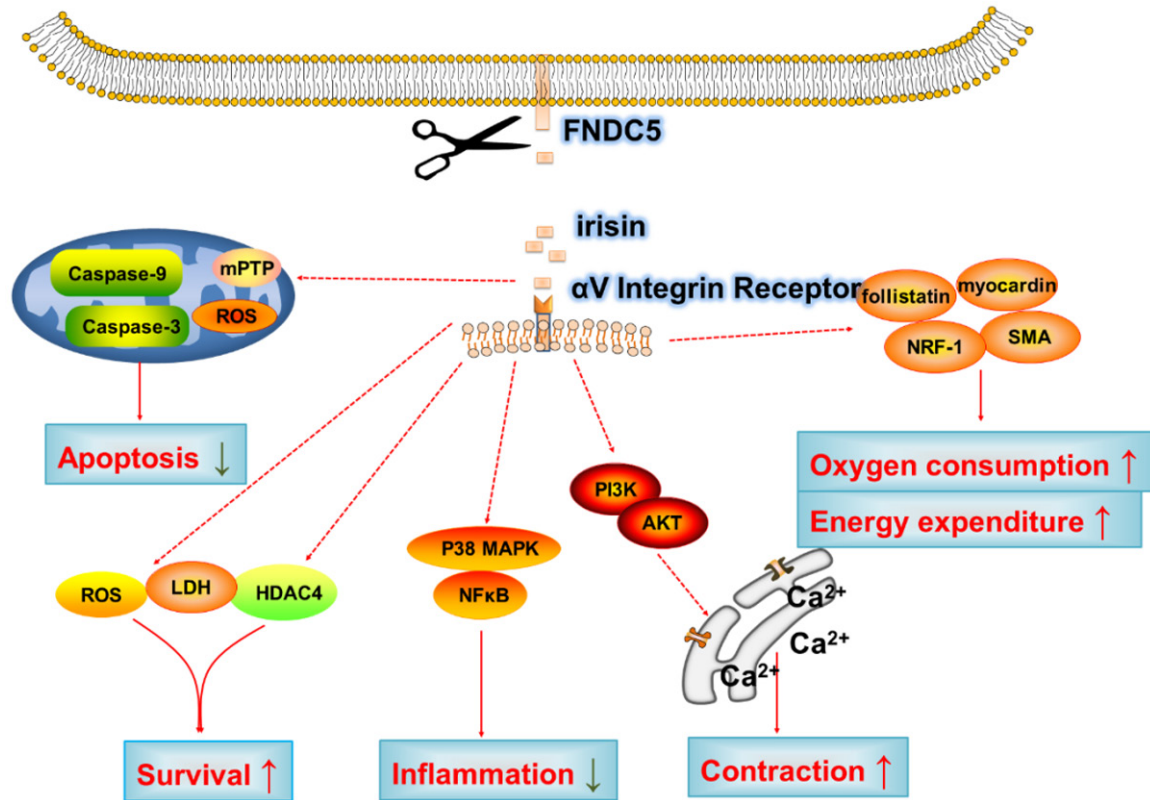


Figure 2. Mechanism of irisin in heart failure. Irisin is a myokine that is cleaved from fibronectin type III domain-containing protein 5 (FNDC5). Irisin influences different activities, such as apoptosis, survival, inflammation, contraction and metabolism. (ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; LDH, lactate dehydrogenase; HDAC4, histone deacetylase 4; P38 MAPK, p38 mitogen-activated protein kinase; NF- κ B, nuclear factor-kappa B; PI3K, Phosphoinositide 3-kinase; AKT, protein kinase B; NRF-1, nuclear respiratory factor-1; SMA, smooth muscle actin).

respiration rate, higher oxygen consumption rate, and increased ROS production were subsequently observed. An *in vivo* study also revealed that irisin treatment in cardiomyocytes enhanced cell apoptosis and cleaved-caspase nine production under hypoxic conditions [63]. Although excessive irisin levels might lead to mitochondrial overdrive and excessive ROS production, we should note that overexpression of genes through viral transduction could elevate the gene expression thousands of times higher than the physiological situation, and the result should be interpreted with caution. In osteocytes and fat cells, the physiological role of irisin is facilitated by α V integrin receptors [64]. However, the signaling pathways of irisin in cardiomyocytes are largely unknown. Integrins and integrin-associated proteins are expressed both in cardiomyocytes and fibroblasts and are involved in cardiac remodeling processes, such as hypertrophy

and fibrosis [65, 66]. Identifying the receptor(s) for irisin on the surface of cardiomyocytes and cardiac fibroblasts will facilitate the understanding of its signaling pathways and aid in the development of therapeutic targets.

Human studies of irisin levels and heart failure are also complicated. Lecker et al. studied patients with systolic HF (LVEF \leq 40%) who underwent aerobic cardiopulmonary exercise at either high or low performance (as evaluated by oxygen consumption) and found that the expression of FNDC5 and PGC-1 α genes in skeletal muscle is positively correlated with aerobic exercise performance in patients with heart failure [67]. This was the first study in humans on the expression of FNDC5 and heart failure. Aronis et al. conducted a nested case-control study to determine whether circulating irisin levels could serve as a biomarker for patients with acute coronary syndrome (ACS)

without successful results. However, interestingly, these researchers found that increased irisin levels are associated with the development of major adverse cardiovascular events (MACE) in patients with established coronary artery disease after percutaneous coronary intervention (PCI) [68]. Shen et al. found that acute heart failure patients with higher serum irisin had significantly higher 1-year all-cause mortality [11]. Kalkan et al. assessed the association between serum irisin levels and cardiac cachexia in heart failure patients with reduced ejection fraction. Serum irisin levels were significantly increased in the cachexia group compared with controls. Serum irisin levels were positively correlated with brain natriuretic peptide (BNP) levels and New York Heart Association (NYHA) class and negatively correlated with body mass index (BMI) and serum albumin levels [69]. Silvestrini et al. conducted a pilot study to evaluate circulating irisin levels in heart failure patients with both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) and found that irisin was significantly increased in HFpEF than in HFrEF patients (7.72 ± 0.76 vs 2.77 ± 0.77 ng/ml, respectively). Total antioxidant capacity (TAC) was introduced as an index of oxidative stress, and an inverse correlation between irisin and TAC was found in HFpEF but not in HFrEF [12].

To date, it remains unknown whether the alteration in irisin levels is the “trigger” for heart failure or merely a “consequence” of heart failure. The answer could even be both given that the heart might be both the recipient and the generator of irisin. The body upregulates its circulating irisin levels to meet the increased energy requirement due to obesity or to compensate for energy deficiency caused by diabetes. High-level irisin stimulation improved cardiac performance together with increased ROS production. In this case, a high irisin level might lead to heart failure. On the other hand, for patients with advanced heart failure whose motor functions have been greatly restricted, the reduction in muscle-derived irisin is inevitable. Thus, the heart increases its irisin production and secretion to improve energy production but potentially also exacerbates cardiomyocyte apoptosis and cardiac fibrosis. Based on the heterogeneity in the etiology of heart failure and the abovementioned influence of age in circulating irisin levels, a more profound cohort

study with strata at different age and etiology levels should be performed to uncover the role of irisin in the heart failure population.

Future perspective

Present studies have demonstrated that irisin has an extensive repertoire of function in the cardiovascular system and might be a promising pharmacological target for cardiovascular diseases. Irisin is involved in glucose/lipid homeostasis, endothelial function, cardiac hypertrophy, and neuro-muscular crosstalk. Given that muscular fatigue and exercise intolerance are common clinical symptoms of heart failure, especially in HFrEF patients, an association among energy production, skeletal muscle abnormalities, and progress of heart failure should be established. However, a long latent period is noted before the heart completely decompensates and produces clinical symptoms. Irisin could be a double-edged sword in heart failure. Exogenous administration of irisin at the early stage of heart failure might be beneficial because it might help energy homeostasis and improve cardiac performance. On the other hand, as learned from clinical studies, an increased irisin level might be related to an increased mortality rate because increased energy expenditure and ROS production could be detrimental in this population.

Thorough studies, both basic research and clinical studies, are needed to fully elucidate the controversies of the exact role of irisin in heart failure. Through basic research, we would like to understand the following: 1) Physiological function of irisin in the cardiovascular system; 2) Mechanism of irisin in cardiac cells, such as cardiomyocytes and endothelial cells; 3) The appropriate timing and dosage for irisin administration *in vitro* and *in vivo*? Through clinical observations, we have to address the following questions: 1) How do irisin levels change in response to heart failure with different etiologies? 2) Can irisin levels be applied as a biomarker for the prevention, diagnosis and prognosis prediction of heart failure? 3) Could behavioral or pharmaceutical interventions be used to prevent heart failure by regulating irisin? With continued progress in understanding the role and mechanism of irisin in the heart, we believe that irisin will play a central role in the management of heart failure in the future.

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Disclosure of conflict of interest

None.

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